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(54) Title: GALLIC ACID DERIVATIVE, AND PHARMACEUTICAL COMPOSITIONS CONTAINING IT

(57) Abstract

3-(2-Ethyl-6-methyl)pyridyl 3,5-dimethoxy-4-ethoxycarbonyloxybenzoate hydrochloride, a process for the preparation thereof, pharmaceutical compositions containing them and the use thereof in human therapy.

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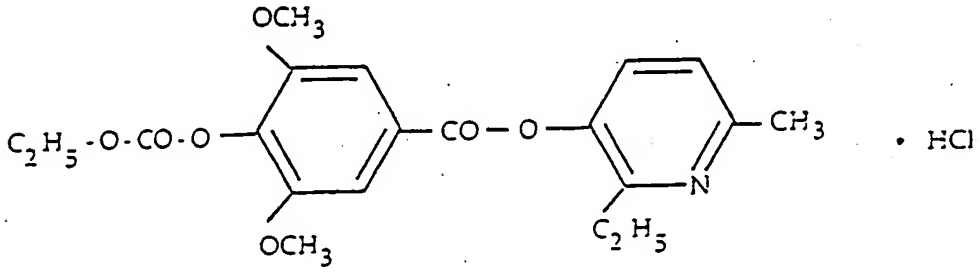
Gallic acid derivative, and pharmaceutical compositions containing it.

The present invention relates to 3-(2-ethyl-6-methyl)pyridyl 3,5-dimethoxy-4-ethoxy-carbonyloxybenzoate hydrochloride of formula



a process for the preparation thereof, pharmaceutical compositions containing it and the use thereof in human therapy.

The compound of the invention, which hereinafter will be named YS-019, is an ester of 3-hydroxy-2-ethyl-6-methylpyridine, which is also known under the name emoxipin.

Emoxipin is a compound which is structurally analogous to vitamin B_6 and has antioxidant activity (R.G. Glushkov, Drugs of the Future vol. 12, No. 8 pages 754-755 (1987)).

Due to an activity inhibiting the action of the free radicals on membrane phospholipids, emoxipin exerts an effective stabilizing action on the biological membranes; particularly on hematic cells.

Said compound is useful in various eye pathologies, such as central chorioretinal dystrophy,

Stargardt's disease, diabetic retinopathy and the like.

Now, it has been found that, by esterificating emoxipin with gallic acid (3,4,5-trihydroxybenzoic acid) derivatives, a product is obtained having surprising pharmacological activities.

Particularly, compound YS-019 of the invention proved to be particularly effective against inflammations, above all against arthritic diseases.

Compound YS-019 was subjected to the following pharmacological tests:

- Antiinflammatory activity - carrageenin oedema

In this test, carried out according to the procedure described by Winter C.A. et al. (Proc. Soc. Exp. Biol. Med. 111, 544; 1962), YS-019 proved to have a higher activity than acetylsalicylic acid.

- Adjuvant arthritis

In the adjuvant arthritis in the rat (Newbold B.B. Brit. J. Pharmacol. 21, 127; 1963), after a 15 day oral treatment, YS-019 significantly reduced the damage caused by the induced arthritis.

- Collagenase inhibition

YS-019 turned out to have also a marked anticollagenase activity, according to the test of Hu C.L. et al (Analyt. Biochem. 88, 638-643; 1978).

The compound of the invention is prepared starting from 2-methylfuran, which is reacted with propionic anhydride in the presence of phosphoric acid. The reaction of the resulting 2-propionyl-5-methylfuran with ammonia in anhydrous ethanol gives 2-ethyl-3-hydroxy-6-methylpyridine, which is then esterified with 4-ethoxycarbonyloxy-3,5-dimethoxybenzoic acid.

The reaction of 2-methylfuran and propionic anhydride can be carried out in the absence of a solvent, which presence is not critical as far as it does not interfere in the reaction progress. The acylation reaction proceeds favourably in the presence of a catalyst, preferably phosphoric acid.

The reaction for the preparation of hydroxypyridine from 2-acylfuran and ammonia is known in literature (P. Bosshard, C.H. Eugster, Adv. Heterocycl. Chem. 7, 377 (1966)).

In a preferred embodiment of the invention, this step is carried out in absolute ethanol as the solvent for gas ammonia and in the absence of NH_4Cl.

The reaction is preferably carried out in autoclave at high temperature, but the reaction can be effected also under different conditions, without departing from the spirit and scope thereof. Attention must be paid to shield acylfuran from light during all of the various steps of the process, to prevent photodegradation.

The final reaction step consists in the preparation <u>in situ</u> of 4-ethoxycarbonyloxy-3,5-dimethoxybenzoic acid, before adding the previously prepared hydroxypyridine, in order to protect the phenol group at the 4-position. For this purpose, syringic acid (4-hydroxy-3,5-dimethoxybenzoic acid) is reacted with ethyl chlorocarbonate.

The reaction is preferably carried out in an inert solvent, such as a ketone or an aliphatic ether, for example acetone or methylisopropylketone. An acid-binding agent, such as an organic amine, for example

trimethyl- or triethylamine, is generally used during the reaction. The reaction must be carried out under inert atmosphere, for example in nitrogen, helium or argon.

Using ethyl chlorocarbonate in a suitable molar ratio to syringic acid (at least 2:1), the phenol group can be protected and the carboxy group can be activated, through formation of the mixed anhydride.

Alternative routes can be followed in order to activate the carboxy group, for example other mixed anhydrides or, even better, acid halides, such as the chloride, can be used.

The products from the single reactions can be recovered by means of conventional techniques, such as distillation, crystallization or preparative chromatography.

The final hydrochloride is obtained by salification in anhydrous medium.

The following example further illustrates the invention.

EXAMPLE

3-(2-Ethyl-6-methyl)pyridyl 3,5-dimethoxy-4-ethoxycarbonyloxybenzoate

1) 2-Propionyl-5-methylfuran

85% Phosphoric acid (3.6 ml; 0.05 mole) is slowly dropped into a mixture of 2-methylfuran (33.05 g; 0.3 mole) and propionic anhydride (78.1 g; 77.3 ml; 0.6 mole) heated to 40°C. The reaction mixture is heated to 60°C for 2 hours. Temperature is allowed to reach the room's one, then 120 ml of water are added, stirring for 1 more hour.

The organic phase is separated and treated with a sodium carbonate saturated solution, stirring for 24 hours, to destroy the unreacted anhydride and acid. After that, the solution is extracted with chloroform (300 ml x 3), then the combined organic phases are dried (Na_2SO_4) and evaporated to obtain an oily residue which is distilled under vacuum, recovering the fraction boiling at 53-56°C (0.6 mm). The pure ketone is obtained (18.7 g; 45%); n_D 1.5050; Rf - 0.22 (toluene - AcOEt 95:5). The product is photosensitive.

2) 2-Ethyl-3-hydroxy-6-methylpyridine

An ammonia saturated solution in absolute ethanol (50 ml), obtained at -15, -20°C, is placed into an autoclave, then the above prepared ketone (50 g; 0.36 mole) is added thereto. The reaction mixture is heated to 170°C for 15 hours, with stirring.

After cooling, ethanol is evaporated off under reduced pressure to obtain a brown solid residue which is taken up into a 2N sodium hydroxide solution (400 ml). After stirring and thoroughly triturating, the alkali solution is extracted with chloroform (100 ml x 4) to recover the unreacted ketone (11 g. about 22%). The alkali liquors are neutralized with concentrated hydrochloric acid, to separate 2-ethyl-3-hydroxy-6-methylpyridine, which separation is completed after cooling overnight (25 g).

Mother liquors are extracted with chloroform (200 ml x 8) and the organic extracts are washed with some water, dried (Na_2SO_4), filtered and evaporated to give more product (7 g). The two solid fractions are combined and repeatedly treated with anhydrous ether

(250 ml x 6) to separate the present chloride(about 2.5 g).

From the ether solution, during concentration, the pyridine derivative progressively crystallizes (30 g; 78%); Rf - 0.33 (AcOEt) - Purity ($HClO_4$) 99.7%; m.p. 171-2°C (not corr.).

3) Title product

Syringic acid (5.95 g; 0.03 mole) is dissolved in anhydrous acetone (70 ml), then triethylamine (8.4 ml; 0.06 mole) is added to the solution. The air is removed under nitrogen stream, which is maintained throughout the whole reaction. The solution is cooled to -10°C, ethyl chlorocarbonate (6.5 g; 5.8 ml; 0.06 mole) is added in about 5 minutes.

This temperature is maintained, stirring for 30 minutes, then the previously prepared hydroxypyridine (42 g; 0.03 mole) dissolved in acetone (50 ml) is added in a single portion. Temperature is left to reach the room's one, then stirring is continued for 4 more hours. After standing overnight, triethylamine hydrochloride is filtered off and the filtrate is evaporated under reduced pressure. The residue is taken up into dichloromethane; then the organic solution is washed with water, 5% sodium hydroxide, water again, then it is dried (Na_2SO_4) and evaporated again to dryness. An oily residue is obtained (9.0 g) which is taken up into boiling absolute ethanol (65 ml); upon cooling and standing, the product crystallizes (8.0 g; 0.02 mole; 68.5%); m.p. 117-9°C; Rf - 0.77 (AcOEt); Rf - 0.17 (syringic acid); Rf - 0.50 (starting pyridine).

The obtained base, dissolved in ethanol and

treated with anhydrous hydrochloric acid in ether, gives the hydrochloride which is crystallized from ethanol to purity (5.0 g; 0.012 mole; 60%); m.p. 183-5°C; titre ($AgNO_3$) - 100.6%.

Elementary analysis for $C_{20}H_{24}ClNO_7$ (425.88)

	C	H	N
calc.%	56.40	5.68	3.29
found.%	56.59	5.66	3.37

The hydrochloride is poorly water soluble.

^{1}H-NMR analysis confirms the expected structure.

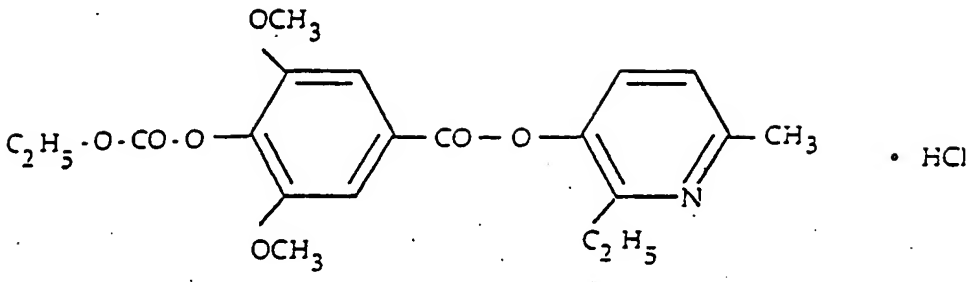
The compound of the present invention can be comprised in pharmaceutical compositions, thanks to the advantageous pharmacological properties thereof. Said pharmaceutical compositions will contain a therapeutically effective amount of compound YS-019 in admixture with conventional carriers and excipients. Said compositions can be prepared according to conventional techniques, such as those described in "Remington's Pharmaceutical Handbook" Mack Pub. U.S.A. Examples of formulations are solid forms, such as tablets, capsules, sugar-coated pills, powders, water-soluble granulates; liquid forms for the enteric or parenteral administrations, such as injectable solutions or suspensions, drops, syrups; topical forms such as ointments, creams and salves; slow-release, sustained-release or gastro-resistant forms.

The present invention also relates to the use of the compound of the invention for the preparation of a medicament for the treatment of degenerative conditions of the connective tissue. Said medicament will contain compound YS-019 in unit or multiple doses, and the

daily dosage will depend on the severity of the condition to treat, as well as on the patient's conditions.

CLAIMS

1. Compound of formula



• HCl

2. A process for the preparation of the compound of claim 1 characterized in that:

a) 2-methylfuran is acylated with propionic anhydride;

b) the resulting 2-propionyl-5-methylfuran is treated with ammonia;

c) the resulting 2-ethyl-3-hydroxy-6-methylpyridine is esterified with 3,5-dimethoxy-4-ethoxycarbonyloxybenzoic acid;

d) the resulting ester is finally transformed into the corresponding hydrochloride.

3. A process according to claim 2 characterized in that step b) is carried out using ethanol as the solvent, in the absence of NH_4Cl.

4. Pharmaceutical compositions containing the compound of claim 1 as the active ingredient.

5. The use of compound of claim 1 as a therapeutical agent.

6. The use of compound of claim 1 for the preparation of a medicament for the treatment of degenerative conditions of the connective tissue.

International App' ›No

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)*

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D213/65; A61K31/44

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D ; A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category°	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	CHEMICAL ABSTRACTS, vol. 105, no. 3, 21 July 1986, Columbus, Ohio, US; abstract no. 17767Q, V.P. ZHERDEV ET AL.: 'Pharmacokinetics of a water-soluble antioxidant of the 3-hydroxypyridine type.' page 10 ; see abstract & BYULLETEN EKSPERIMENTALNOI BIOLOGII I MEDITSINY vol. 101, no. 3, MOSCOW pages 325 - 327; --- -/--	1,5

° Special categories of cited documents:[10]

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
25 JUNE 1992	10.07.92
International Searching Authority: EUROPEAN PATENT OFFICE	Signature of Authorized Officer: P. BOSMA

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III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM ...E SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	CHEMICAL ABSTRACTS, vol. 100, no. 23, 4 June 1984, Columbus, Ohio, US; abstract no. 185352R, G. LIU ET AL.: 'Pharmacological study of gallic acid from Ampelopsis brevipedunculata.' page 21 ; see abstract & NANJING YAOXUEYUAN XUEBAO no. 2, 1983, NANJING, CHINA pages 43 - 47; ---	1,5